



# Challenging the Hypothesized Link to Season of Birth in Patients with Schizophrenia

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## ABSTRACT

The cause of schizophrenia is unknown; however, one hypothesis is that seasonality of birth contributes to its development, with an excess of winter-spring births observed in those with schizophrenia. There are over 200 studies exploring this issue at the writing of this article with most of the studies revealing a decrease in late summer births and an increase number of winter-spring births of those individuals with the disease.

The primary objective of this study was to evaluate the seasonality of birth for 376 institutionalized patients with schizophrenia receiving clozapine treatment in a New York State psychiatric hospital. This was a retrospective review of a clozapine database accessed between January 1, 2001 to January 1, 2011, which included date of birth for the national clozapine registry, confirming the accuracy of the information. The psychiatric diagnoses for the patients included in this study were documented to ensure that this research included individuals with schizophrenia. The author hypothesized that due to the long-term

institutionalization often required for refractory schizophrenia, the New York state hospitalized patients were assumed to be of Northern Hemispheric birth origin. The study sample included 376 patients, 16 of which did not have a definitive diagnosis of schizophrenia. The author chose to evaluate all 376 patients in the sample due to the introduction of clozapine therapy, which would substantiate the presence of a refractory psychotic disorder, such as schizophrenia. The author found that the seasonality distribution did not reflect any difference in percentage from that which would be expected in the general population, challenging the hypothesis that seasonality of birth contributes to the development of schizophrenia. The author provides a review of literature and discusses some of the theories surrounding the season of birth hypothesis. A larger patient sample should be studied to confirm the findings of this smaller population sample.

## INTRODUCTION

Schizophrenia is a complex mental disorder characterized by a number of

**TABLE 1.** Percentage of excess or deficit births pooled from inpatients with schizophrenia born during the years 1925 to 1975 for Ohio (OH), Pennsylvania (PA), Virginia (VA), and North Carolina (NC)<sup>5</sup>

SCHIZOPHRENIA CLASSIFICATION	STATE	DEC	JAN	FEB	MAR	APR	MAY	JUN	JUL	AUG	SEP	OCT	NOV
Schizophrenia, NOS	OH	6.5	3.9	12	6.6	5.5	-2.3	-10.3	-4	-1.6	-2.7	-2.8	-7.1
	PA	10.9	9.3	-3.8	7.9	-8.2	-2.7	-8.5	4.1	0.2	-2.5	0.5	-8.2
	VA	7.7	3.6	3.1	1.6	4.3	2.1	-0.3	8.8	-5.2	-9.2	-5.3	-11.9
	NC	8	7.2	-15.9	-2.8	8.8	-6	-10.8	-0.8	3.4	1	15.9	-10.2
	Total	8.2	5.5	2.3	3.7	3.3	-0.5	-5.7	4.3	-2.7	-5.7	-1.1	-10.1
Schizophrenia, paranoid	OH	9.5	0.9	7.8	1.7	-4.5	-5.5	-6.2	1.2	-3.8	-3.2	-1.3	6.5
	PA	-1.9	7.4	3.4	-2.4	1.1	0.1	1.6	2.8	-5.1	1.9	-7.2	-1.8
	VA	0.4	3.6	5.1	1.3	0.6	-1.3	-6	4.2	-2.4	0.6	-1.4	-6.2
	NC	-5.9	10.2	5.5	17.3	-1.2	-10	-13.5	-3	-14.3	-2.1	-1.1	19.5
	Total	0.9	4.1	5.1	3.7	0	-2.9	-6	2.3	-5	0	-2.5	1.1
Schizoaffective disorder	OH	-4.9	3.1	4.6	6.6	6.4	-3.7	1.5	0.9	-7	-0.9	-3.5	1.2
	PA	4.2	17.3	-3.6	-0.3	-10.1	-1.4	-3.7	0.8	-5.5	2.9	2.5	-3.8
	VA	-3.1	-0.5	0.5	9.1	0.4	2.3	2.4	-4.5	5	-5.6	-9	2.2
	NC	-12.6	6.8	28.3	21.6	6.8	-10.8	-8.4	2.9	-1.2	-10.8	0	-8
	Total	-3	4.8	4	9.3	-1.2	-1.1	-1.2	-1.9	0.1	-3.9	-4.7	-0.1

NOS: not otherwise specified

hallmark symptoms, including both positive symptoms (e.g., delusions, hallucinations, paranoia, and disorganized speech and behavior) and negative symptoms (e.g., alogia, anhedonia, and avolition).<sup>1</sup> Schizophrenia varies in type and severity and is an illness that creates life-long challenges for those diagnosed with the disease. For most patients, the onset of schizophrenia occurs early in life with male individuals typically experiencing initial symptoms in their late teenage age years to early 20s and female individuals typically experiencing an onset of symptoms in their late 20s to 30s. Despite the different ages of onset, schizophrenia affects male and female individuals equally, with approximately one percent of the world's population being diagnosed with schizophrenia.<sup>2</sup> Though the exact cause of schizophrenia remains unknown, research from the last few

decades has provided several findings that have shed some light on areas for further investigation. Genetics and abnormalities in fetal brain development are two prominent factors that have been shown to play a role in this disorder.<sup>1</sup> However, other environmental factors and their influence on the development of this disorder have also been examined. One factor, in particular, that has been postulated is season of birth, with the theory being that birth in the winter and spring months may contribute to the development of schizophrenia. The impetus for this theory was a study by Tramer in 1929, which showed a greater incidence of winter or spring births in patients.<sup>3</sup>

At the writing of this article, there were over 200 studies exploring season of birth as it relates to schizophrenia, with most of the studies revealing a decrease in late summer births and an increase number of winter-spring

births of those individuals with the disease.<sup>4</sup> The objective of this study is to explore the season of birth for 376 patients with schizophrenia within a northern hemispheric psychiatric institution to further contribute to the literature related to this subject. This protocol was approved by the New York State Psychiatric Institute Institutional Review Board.

## LITERATURE REVIEW

Since 1929, numerous studies have been conducted to assess the possible relationship between season of birth and schizophrenia.<sup>3</sup> One of the landmark articles in seasonality of birth and schizophrenia, which reviewed the results of 86 studies in both the northern and southern hemispheres, was written by Torrey et al.<sup>5</sup> The authors of this review found there to be a peak in the number of births of individuals diagnosed with schizophrenia in December to May

**TABLE 2.** Family history of schizophrenia and place of birth in a population study in Denmark<sup>7</sup>

FAMILY HISTORY OF SCHIZOPHRENIA	RELATIVE RISK, %	CI (95%)
Parent		
Both parents	46.9	(17.56–125.26)
Father only	7.2	(5.1–10.16)
Mother only	9.31	(7.24–11.96)
Neither parent	1	1
Mother, father unknown	14.18	(8.48–23.7)
Father, mother unknown	2	(1.72–2.32)
Sibling		
≥One	6.99	(5.38–9.09)
No affected sibling	1	1
PLACE OF BIRTH	RELATIVE RISK, %	CI (95%)
Greenland	3.71	(2.04–6.76)
Other countries	3.45	(2.69–4.44)
Capital Denmark	2.4	(2.13–2.70)
Suburb of capital	1.62	(1.37–1.90)
Town (population <100,000)	1.24	(1.36–1.81)
Unknown	1.22	(0.16–3.27)
Season of birth	1.11	(1.06–1.18)
Rural area	1	1
CI: confidence interval		

with a peak in January and February.<sup>5</sup> The average percent of excess births, which is the difference between observed births compared to expected births, in these months was found to be 5 to 8 percent, with a few studies finding an excess of as much as 11 to 15 percent. The authors did note, however, that there were few studies that were adequately powered to detect a sufficient excess.<sup>5</sup>

One such study, published in 1996, by Torrey, et al<sup>6</sup> examined seasonality trends in schizophrenia and various other psychiatric disorders. *Diagnostic and Statistical Manual for Mental Disorders, Third Edition (DMS-III)* criteria for 71,278 patients

with schizophrenia who were born from 1925 to 1975 and were admitted to state psychiatric hospitals in Ohio, Pennsylvania, Virginia, and North Carolina were used for analysis. Data collected from census information as well as predicted number of births for each psychiatric category were used as comparators to determine the presence and magnitude of excess births for any given month.<sup>6</sup> For paranoid schizophrenia, the average percent of excess of births was 3.4 percent and the highest excess occurred in February with a percent excess of 5.1 percent. For all other types of schizophrenia, the average percent of excess births was five

percent, and the highest excess of births occurred in December with a percentage of 8.2 percent.<sup>6</sup> As shown in Table 1, Torrey shows the percent excess or deficit births for each diagnostic category for each state. In this study, for all four states combined there is an excess number of births in the months December through March (circled in red on Table 1) for individuals with bipolar disorder; schizophrenia, not otherwise specified (NOS); and schizophrenia, paranoid. Though there was documented winter birth excess for those with major psychoses, the actual causal event could have occurred in the first trimester (summer), second trimester (fall), or at conception in the spring.

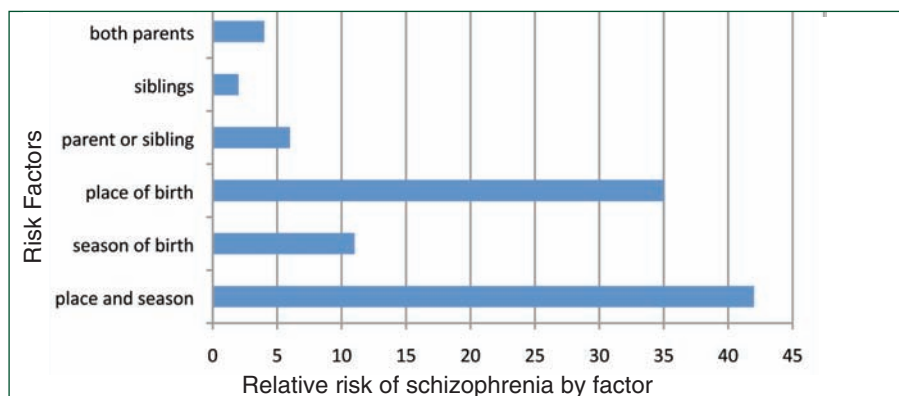
A study conducted by Mortensen, et al<sup>7</sup> followed women born in Denmark from April 1, 1935 to March 31, 1978 and their children.<sup>7</sup> The investigators used *International Classification of Diseases, Eighth Edition (ICD-8)* data from the Danish Psychiatric Central Register to identify the children who went on to develop schizophrenia. A total of 1.75 million children were followed and 2,669 were diagnosed with schizophrenia (Table 2, Figures 1 and 2).<sup>7</sup> The number of subjects was greatest in the birth months of February and March and the amplitude occurred on March 6. The likelihood of birth on this date was calculated to be 1.1 times that of the likelihood of birth in early June or December, and the population attributable risk for season of birth was 10.5 percent.<sup>7</sup> Mortensen's group determined that although a history of schizophrenia in a parent or sibling is associated with the highest risk, the place of birth, as well as the season of birth, account for a significant portion of the relative risks.

In 2000, a study by Parker et al<sup>8</sup> was published that examined the seasonality of birth and schizophrenia in Singapore, which is located slightly north of the equator.<sup>8</sup> Using *ICD* codes obtained from discharge data from a government psychiatric facility, the investigators analyzed birth data for 9,141 patients with schizophrenia who were born between 1930 and 1984.

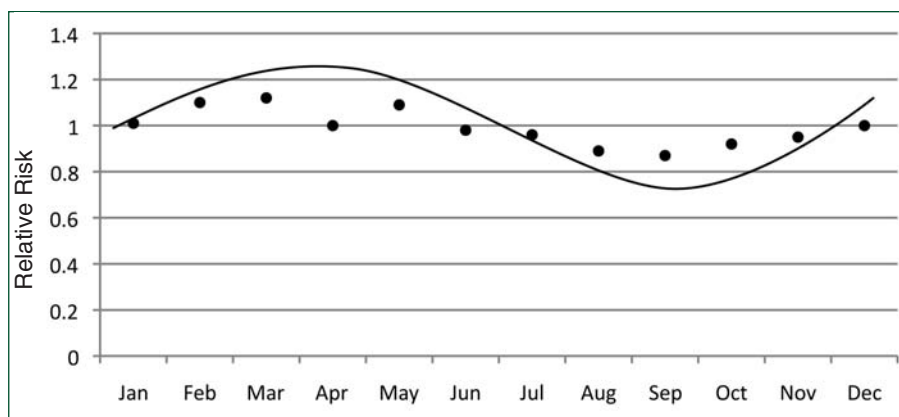
For patients with schizophrenia born from 1930 to 1949 and 1960 to 1984, there were significant peaks of births on October 28 and September 28, respectively. Data analysis for the general population from 1960 to 1984 was also conducted, which revealed a peak of births in early October (Table 3, Figure 3). The number of births for patients with schizophrenia and the general population did not vary month to month with the exception of a lower number of schizophrenia births in March and April; the exact significance of this finding was not addressed by the investigators.<sup>8</sup>

A meta analysis from 2003, which analyzed eight studies pertaining to season of birth and schizophrenia in the northern hemisphere, found that there was a pooled odds ratio (OR) of 1.07 and a population attributable risk of 3.3 percent for winter/spring birth.<sup>9</sup> The authors also found a significant positive correlation between the OR of winter/spring birth and latitude, and the seasonality of schizophrenia births varied by latitude band. Conversely, a southern hemisphere meta analysis was also conducted in 1999, which looked at 11 studies and failed to find a significant excess in any month.<sup>10</sup>

Although many investigators speculate on the causes of the excess number of births in the winter/spring months, few have found a definitive explanation. An article published by Tochigi et al<sup>11</sup> evaluated studies that sought to identify the mechanism behind this apparent seasonal effect. One possible factor that has been put forth in a small number of studies is meteorological changes, such as temperature, rainfall, humidity, and hours of sunshine during pregnancy. The researchers evaluated their data using linear regression of the OR by latitude. The correlation gave a significant slope that corresponded to approximately 0.02 percent increase in odds per 10 degrees increase in latitude. When the equatorial region of Singapore was removed from the analysis, the slope became attenuated. Very few studies have been able to detect a correlation between these factors and an excess of winter/spring



**FIGURE 1.** The relative risk of schizophrenia established by Moretson et al.<sup>7</sup> History of schizophrenia in a parent or sibling was associated with the highest risk, with place of birth and season of birth accounting for a significant portion of the relative risks.



**FIGURE 2.** Relative risk of schizophrenia according to the month of birth (Mortenson et al).<sup>7</sup> Investigators depict their data with points and vertical bars documenting the relative risks and confidence intervals (95%) with the month of birth analyzed as a categorical variable. The curve reflects the relative risk as a function of the reference category as the month of December.

birth in schizophrenia, which may be due to small patient populations used in the studies.<sup>11</sup>

## METHODS

For this study, retrospective database reviews were conducted (N=376) on inpatients at a state psychiatric inpatient facility for those receiving clozapine. Only patients using clozapine were included in this population sample, as other patients receiving alternative therapy generally did not have refractory schizophrenia exclusively as the diagnosis. See Figure 4 for the diagnoses listing for patients included in our sample.

## RESULTS

This was a retrospective database review of the 376 psychiatric inpatients taking clozapine within the

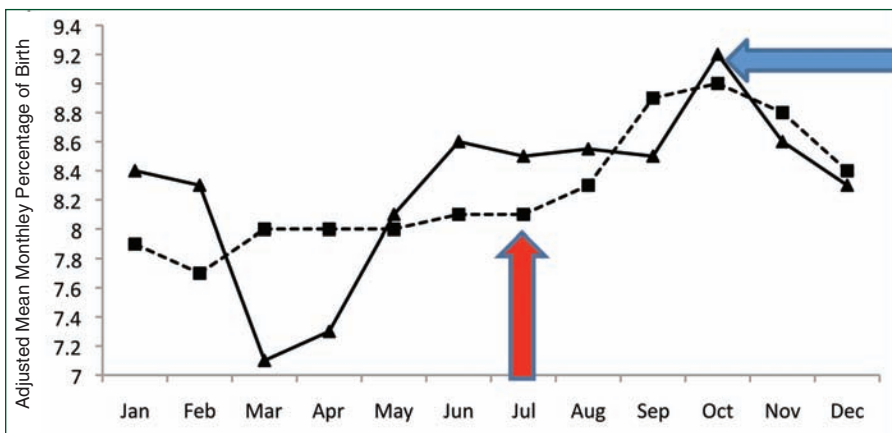
study time period of January 1, 2001 to January 1, 2011. No correlation coefficient was used, as the breakdown of the seasonal births required only an analysis of the percentage based on dates.

The author found that the seasonality distribution did not reflect any difference in percentage from that which would be expected in the general population. The data showed that the percentage of winter births was the same as spring and less than summer.

## DISCUSSION

Though season of birth has been considered as a potential link to schizophrenia, seasonality has also been demonstrated in other mental health disorders, such as bipolar disorder and major depression. Torrey



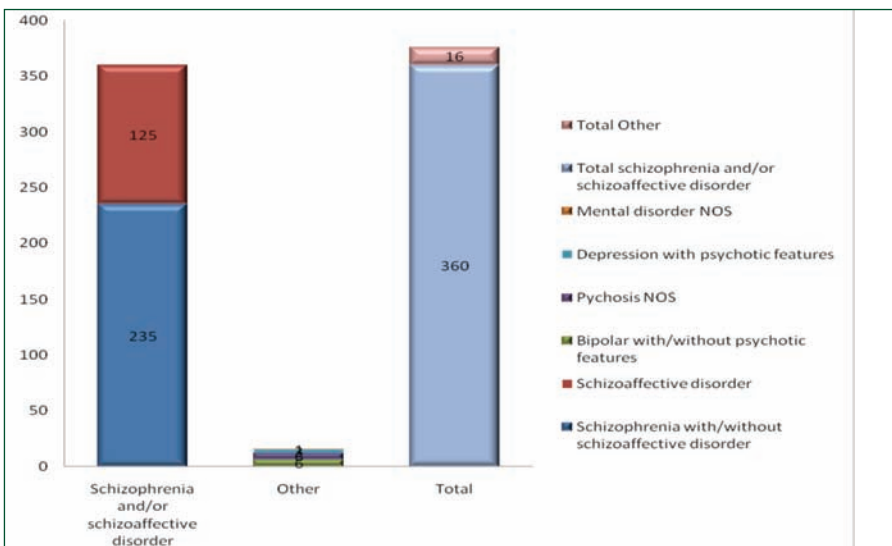


**FIGURE 3.** Adjusted mean monthly percentage of birth for patients with schizophrenia compared with general population. Parker et al<sup>8</sup> demonstrated that despite the equatorial nature of the environment in Singapore, this region did show a seasonal difference between those births for patients with schizophrenia and for the general population. The peak of births for this region was the fall. The blue arrow indicates those with schizophrenia; the red arrow indicates the general population.

**TABLE 3.** Data collected from Singapore, a city near the equator. There is a peak of all births for the fall season, suggesting a seasonal date of conception during the holidays where procreation may be more likely (December-January) with holiday time spent with family (Parker et al).<sup>8</sup>

BIRTHS	PERIOD, YEARS	N	DATE OF PEAK	CI (95%)	P-VALUE
Patients with schizophrenia	1930–49	2,701	28-Oct	Sep 30–Nov 17	<0.001
	1950–59	3,046	30-Sep	N/A	N/A
	1960–84	3,393	28-Sep	Aug 16–Nov 3	<0.01
Total	1930–84	9,141	14-Oct	Sep 19–Nov 8	N/A
All live births	1960–69	55,197	3-Oct	Sep 28–Oct 9	<0.001
	1970–84	643,810	1-Oct	Sep 30–Oct 4	<0.001
Total	1960–86	1,195,007	2-Oct	Sep 30–Oct 4	N/A

CI: Confidence interval

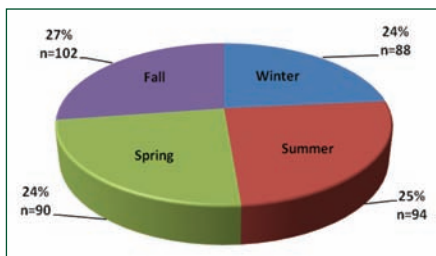


**FIGURE 4.** Diagnosis breakdown

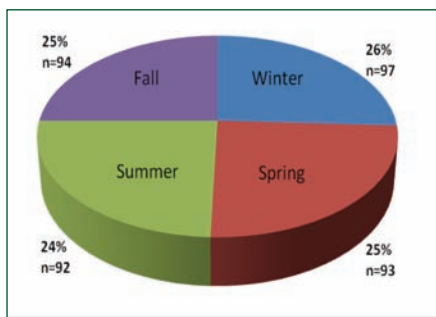
et al<sup>8</sup> found that there was a significant coherence found between schizophrenia, paranoid type, and bipolar disorder, both of which were found to have an excess of winter births, whereas depression had an excess of spring births. For this reason, it is critical that researchers continue to explore factors related to season as a focus for further investigation. The link of season of birth may be related more to the season of conception rather than the month of birth. Figures 5, 6, and 7 reflect the author's data based on 36-week and 40-week gestational periods, and though the author did see a similar pattern of percentage distribution, the recorded seasonal differences may actually be a result of entirely different factors than hypothesized as a result of "winter" birth. One factor not yet considered may be environmental toxins, which would be more widely dispersed in the warmer months of conception (e.g., lawn chemicals, pesticides).

One of the current considerations in the literature is the exposure to sunshine and the implication to the production of vitamin D, which is dependent upon the action of the sunlight on the skin.<sup>12</sup> Ultraviolet B radiation acts on a cholesterol metabolite in the epidermal layer of the skin leading to the production of Vitamin D. Further hydroxylation of vitamin D in the liver and then the kidney results in 25-hydroxyvitamin Dc (25(OH) D3) as the active form of vitamin D. The health consequences of low serum concentrations of vitamin D have become more evident, including rickets, osteomalacia, and neuropsychiatric disorders.<sup>10</sup> The prevalence of hypovitaminosis D as a common lab finding for patients with schizophrenia received some indirect support from a Finnish birth cohort study;<sup>10</sup> however, to date there is no study that has examined the direct association of neonatal vitamin D levels and schizophrenia.

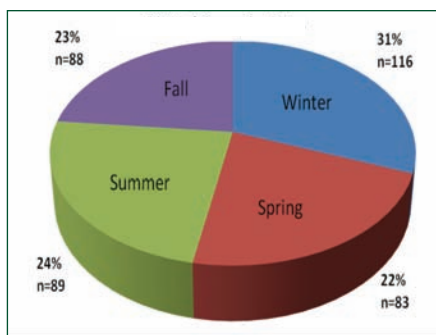
Another leading hypothesis is the influence of infection during pregnancy. In a meta analysis that examined studies on seasonality and



**FIGURE 5.** Definitions for New York seasons—fall: September, October, November; winter: December, January, February; spring: March, April, May; summer: June, July, August



**FIGURE 6.** Seasonality distribution based on 40-week conception dates—fall: September, October, November; winter: December, January, February; spring: March, April, May; summer: June, July, August



**FIGURE 7.** Seasonality distribution based on 36-week conception dates—fall: September, October, November; winter: December, January, February; spring: March, April, May; summer: June, July, August

birth in patients with schizophrenia, Tochigi et al<sup>11</sup> found many studies that examined links between infections during pregnancy and schizophrenia. Many of these studies found positive results and timing of the infection during the course of the pregnancy in terms of trimester and was also a factor of increased risk of schizophrenia.<sup>11</sup> Tochigi et al also found

through their meta-analysis that, in addition to vitamin D deficiency, other possible causes of schizophrenia have been studied, such as deficiencies in vitamin C, low maternal zinc, and high maternal copper during pregnancy as well as variations in maternal estrogen. Currently, there exists no well-defined explanation for the seasonality observed in schizophrenia, and many studies continue to examine a large number of varying hypotheses.

## CONCLUSION

While family history of schizophrenia is the best established risk factor for schizophrenia,<sup>7</sup> there are related factors that should warrant future research. The author recommends that further research on the etiology of schizophrenia focus on maternal pharmacokinetics of medications prescribed during pregnancy, especially for mothers diagnosed with schizophrenia or other mental disorders. Untreated maternal illness has been well known to cause complications in the newborn.<sup>7</sup> In hemispheric births occurring in the winter (January through March), spring conception coupled with medication changes (pharmacokinetic or pre-emptive by conservative providers) in mothers with schizophrenia warrants more investigation.

A larger patient sample should be studied to confirm the findings of our smaller population, which challenges the hypothesis of seasonality in schizophrenia. In light of the absence of predicted seasonal differences in births of the individuals in our study sample, alternative sources of risk for development of schizophrenia warrant further exploration and investigation.

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